NATIONAL MARROW DONOR PROGRAM®

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QUARTERLY
PERFORMANCE / TECHNICAL REPORT
for
APRIL 1, 2006 to JUNE 30, 2006

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for
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Office of Naval Research

And

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1. Contingency Prepardness: Collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

2. Rapid Identification of Matched Donors : Increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

3. Immunogenetic Studies: Increase understanding of the immunologic factors important in HSC transplantation.

4. Clinical Research in Transplantation: Create a platform that facilitates multicenter collaboration and data management.

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Development of Medical Technology for Contingency Responses to Marrow Toxic Agents

Quarterly Performance / Technical Report

April 1, 2006 – June 30, 2006

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IID.1.3	Expand Immunobiology Research	Included

A. CONTINGENCY PREPAREDNESS

The primary goals of this project are to collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

Hypothesis 1 - Recovery of casualties with significant myelosuppression following radiation or chemical exposure is optimal when care plans are designed and implemented by transplant physicians (A.1)

Efforts of these Aims are to engage transplant physicians in additional planning efforts to include opportunities to participate on subcommittees that will address specific, critical aspects of a contingency response plan.

Aim 1 (A.1.1)
Continue to secure the interest and participation of transplant physicians.

Activity:
In June an Emergency Preparedness Web page was added to the Network website. This Web page provides a location for centers and NMDP staff to look to for information on radiation related emergency management incidents. The following information is available on the Web page:

- Emergency Preparedness Related Network Web site Resources
- NMDP FAQ/info sheets
- Radiation related information
- Fact sheets
- Radiation Pocket Guides & Flyers
- Links to sites of interest
- Free training sites
- Streaming videos of interest
- General information of possible interest
- Downloads
- Pandemic health information (a.k.a. Bird Flu)
- Personal preparedness

A Core Contingency Network (CCN) meeting is being planed for August 31, 2006 in Chicago. During this meeting the group will discuss patient preparatory regimens, data collection plans, and search criteria.

Aim 2 (A.1.2)

Refine protocols for patient assessment and use of GCSF in radiation exposure situations.

Activity:
No reportable activity this period.

Aim 3 (A.1.3)

Refine guidelines for patient assessment, product selection and transplant in radiation exposure situations.

Activity:
The activity related to the National Library of Medicine (NLM) web based ARS treatment guidelines (Aim2) furthers the development related to this aim. During this period Core Contingency Network physicians reviewed the Website and provided feedback for improvements.

The further development of the radiation victim preparatory regimen and search criteria were discussed on April 10, 2006 with Dr. Confer, Dr. Chao and Dr. Weisdorf. From this teleconference the working group decided to further develop these areas for presentation to the Core Contingency Network physicians at the August 31st meeting in Chicago.

IS efforts on this Aim focused on support of the processes and tools utilized by the Search and Transplant department at NMDP.

One way in which this is done is through the daily support of the Search and Transplant department. Search and Transplant staff is responsible for troubleshooting and resolving any issues preventing product selection being made, as well as any issues encountered en route to a successful transplant. Search and Transplant is also responsible for helping to refine new processes and maintain data integrity until those processes are fully supported by software.

The SEARCH Link™ V2.5.0 and TRANS Link® V4.5.0 applications were upgraded on April 30, 2006. The main focus of this upgrade was to implement changes for the Cord Blood Confirmatory Typing Packages.

For STAR II, work has focused on the receipt of XML transactions from various parties. This was first implemented for the NMDP Web Scripts, which allow international centers to submit search related data. Along with this enhancement, international centers now have the ability to submit PBSC data electronically to the STAR system. Work is also underway to convert messaging between STAR and STAR Link to XML as well. XML transactions will allow for greater flexibility and will help ensure that messaging between systems remains nimble as

business processes evolve. Lastly, early design discussions have begun for the support of Forms Net 2.0 transactions to the STAR system.

Aim 4 (A.1.4)

Define and develop a national data collection and management model.

Activity:
The further development of the data collection plan was discussed on April 10, 2006 with Dr. Confer, Dr. Chao and Dr. Weisdorf. From this teleconference the working group decided to further develop these areas for presentation to the Core Contingency Network physicians at the August 31st meeting in Chicago.

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Development of Medical Technology for Contingency Responses to Marrow Toxic Agents

Quarterly Performance / Technical Report

April 1, 2006 – June 30, 2006

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A. CONTINGENCY PREPAREDNESS

The primary goals of this project are to collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

Hypothesis 2 - Coordination of the care of casualties who will require hematopoietic support will be essential in a contingency situation. (A.2)

Efforts of these Aims will be to enhance the NMDP's ability to respond to casualties of a radiation exposure.

Aim 1 (A.2.1)

Develop a permanent organization of transplant centers to maintain a contingency response network.

Activity:
During this period Core Contingency Network participation was confirmed for another transplant center. This brings the total participating transplant centers to 12 of the 15 initially invited to join the Core Contingency Network. These centers are:

1. Seattle, WA-Seattle Cancer Care Alliance
2. Houston, TX-M.D. Anderson Cancer Center
3. Boston, MA-Dana Farber/Partners Cancer Care
4. Duarte, CA-City of Hope National Medical Center
5. St. Louis, MO-Barnes-Jewish Hospital at Washington
6. Durham, NC-Duke University Medical Center
7. Philadelphia, PA-University of Pennsylvania Medical Center
8. NY, NY-Memorial Sloan-Kettering Cancer Center
9. Houston, TX-Texas Children's Hospital
10. Cincinnati, OH-Cincinnati Children's Hospital Medical Center
11. Minneapolis, MN-University of Minnesota BMT Program
12. Denver, CO-Presbyterian/St. Lukes Medical Center

The NMDP continues to work with the remaining three centers that have not confirmed involvement in the Core Contingency Network.

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Development of Medical Technology for Contingency Responses to Marrow Toxic Agents

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August 1, 2005 – September 30, 2005

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Aim 2 (A.2.2)

Develop and test standard operating procedures, in conjunction with core transplant centers, to manage the activities required to HLA type siblings of casualties to evaluate their potential as HSC donors for their affected family member.

Activity:

The working group held a meeting to identify requirements of an integrated system for management of sibling typing. The group determined a possible means for this process to integrate with current operations. This group will continue to develop the process.

Government Signature _____ Date _____

A. CONTINGENCY PREPAREDNESS

The primary goals of this project are to collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

Hypothesis 3 - NMDP's critical information technology infrastructure must remain operational during contingency situations that directly affect the Coordinating Center. (A.3)

Efforts of this Aim will be to establish a functional disaster recovery site, enable real time replication of critical data systems, and configure disaster recovery site to be managed and operated remotely from the NMDP's Minneapolis Headquarters.

Aim 1 (A.3.1)

Ensure NMDP's ability to access and utilize its information management and communication infrastructure in a contingency situation in which its Minneapolis Coordinating Center is damaged or destroyed.

Activity:

The Business Continuity Planner reviewed the existing organization business continuity plan and updated the critical staff and equipment requirements. This sets the groundwork for progressing with the evaluation of the most effective means for a staff recovery facility.

Additional network bandwidth was purchased, configured, and deployed to the Kansas disaster recovery site. This bandwidth was prerequisite to remotely operate and manage the site from NMDP's Minneapolis or New Brighton, Minnesota facilities and for the future step of enabling real time replication of critical data. Disaster Recovery Test #16 was conducted beginning on April 10, 2006 and lasted 48 contiguous hours. This test utilized the additional bandwidth by VPN between Kansas and New Brighton. As a result, only 3 staff members were required to fly to the Kansas data center while all others, including applications users that participated in users testing conducted their work from New Brighton, MN.

B. Development of Science and Technology for Rapid Identification of Matched Donors

The primary goal of this project is to increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

Hypothesis 1 - Increasing the resolution and quality of the HLA testing of volunteers on the registry will speed donor selection. (B.1)

Efforts of these Aims are to increase the register diversity, evaluate HLA-DRB1 High Res Typing, evaluate HLA-C Typing of donors, and evaluate buccal swabs.

Aim 1 (B.1.1)

Expand the genetic diversity of the Registry through continued addition of adult donors and cord blood units, utilizing high volume HLA typing methodologies.

Activity: Five laboratories performed HLA-A, B, DR typing of 23,955 newly recruited volunteer donors. The network of laboratories was monitored using blind quality control samples to ensure that high quality typing results were received. The error rate for the quality control samples was determined for each laboratory, by month, for HLA-A, B (class I) and HLA-DR (class II). For this period, the average error rate using standardized membrane bound SSOP core approach, One Lambda Luminex-based SSO and sequence based testing (SBT) was 0.30%. The error rate was below the project requirement of less than or equal to 1.5%.

The laboratories' turnaround time criteria specify that 85% of the class I and class II results must be reported within 14 days. Ninety-six percent of the HLA-A, B results and 98% of the HLA-DR results were reported within 14 days.

Aim 2 (B.1.2)

Evaluate the impact on the typing process, cost and donor selection of high resolution DRB1 testing of new volunteers. Utilize high resolution data generated to optimize allele and haplotype frequency calculations.

Activity: No Activity

Aim 3 (B.1.3)

Evaluate the impact of HLA-C typing donors and develop a strategy for future recruitment typing that will optimize identification of the best matched donors for patients.

Activity: No Activity

Aim 4 (B.1.4)

Evaluate the suitability of buccal swabs as a method to collect DNA samples to HLA type casualties and potential related donors in contingency situations, and to obtain research samples.

Activity: Donor centers and recruitment groups began implementing the collection of buccal cells onto cotton swabs for the majority of new volunteer donors in April 2006. The NMDP Repository transitioned to this new sample type and the HLA contract laboratories have successfully typed 99.85% of 20,834 buccal swabs tested. This method has proven to be very successful for the NMDP, contract laboratories, donors and our Network.

The initial design of the buccal swab bar code label proved to be difficult to process at the Repository and HLA contract laboratories. A team worked to redesign the labels to improve functionality.

DNA was extracted from quality control (QC) frozen whole blood samples and cotton swabs dipped into the solution in order to provide blind QC buccal swab samples to ship to the laboratories.

B. Development of Science and Technology for Rapid Identification of Matched Donors

The primary goal of this project is to increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

Hypothesis 2 - Primary DNA typing data can be used within the Registry to improve the quality and resolution of volunteer donor HLA assignments (B.2)

Efforts of these Aims are to collect, validate, and reinterpretate primary data so as to interprert this data against genotype lists and matching algorithms.

Aim 1 (B.2.1)

Retrospective and prospective collection of supplemental primary data to complete the donor records in the interpretation database.

Activity:
During the past quarter software to process HML 0.3 messages was developed. This version allows genotype list data to be reported directly without the need to compress to multiple allele codes. SBT typing data can be processed and stored for future validation.
This also allows primary data to be collected and utilized in the matching algorithm for cord blood units.
Only one new kit version was registered but data processing of primary data from contract recruitment typings is proceeding smoothly for the defined kits.

Aim 2 (B.2.2)

Validation of the logic utilized for interpretation of HLA-A and B primary data to ensure accuracy of this approach prior to integration into the NMDP matching algorithm.

Activity:
Approximately 29, 057 donors that had been typed for DRB1 high resolution in 2003 were utilized to perform validation of the HapLogic predictions at DRB1, Pr(6), and Pr(5) for AB only typed donors. Cases where there were mismatches at the A and B loci, or where results were indeterminant were removed from this pool. A statistically significant number of 76 was calculated from the 23,332 remaining donors. The 76 cases were randomized prior to evaluation.

In addition to the 76 random cases, two sets of specific cases were reviewed:

1. Cases where the probability of 6/6 allele match (Pr(6)) prediction was high[1], but the actual results did not match - 10 cases
2. Cases where the Pr(6) prediction was low[2], but the actual results matched - 82 cases

- Cases where Pr(6) prediction was low, and the probability of 5/6 allele match (Pr(5)) prediction was high and actual results matched- 18 cases
- Cases where Pr(6) prediction was low, and the Pr(5) prediction was low and actual results matched- 64 cases identified

[1] A Pr(6) or Pr(5) prediction of greater than 50% was considered a "high" prediction.
[2] A Pr(6) or Pr(5) prediction of less than 50% was considered a "low" prediction.

The scientific services validation team reviewed each case described above with the following results:

- 76 random cases- 91% of the predictions were within the anticipated range, 9% of cases were outside of the anticipated range
- 10 Cases where the Pr(6) prediction was high, but the actual results did not match - 100% of predictions were within the anticipated range
- 18 Cases where Pr(6) prediction was low, and the Pr(5) prediction was high and actual results matched- 50% of predictions were within the anticipated range and 50% of predictions were outside of the anticipated range
- 64 Cases where Pr(6) prediction was low, and the Pr(5) prediction was low and actual results matched- 66% of predictions were in the anticipated range and 34% of predictions were outside the anticipated range

All predictions which were not satisfactory were logged. Final resolution of predictions which fell outside of the anticipated range are under investigation by the bioinformatics working group.

Aim 3 (B.2.3)

Reinterpretation of primary data to improve the level of resolution of previously reported donor typings.

Activity:
Work is ongoing to make more data available for DRB1 and replace generic (XX) multiple allele codes for Class I typings with NMDP codes derived from these genotype lists for display on search reports. During the past quarter testing of the matching algorithm was performed and a migration process was developed for moving the remainder of the primary data into utilization in the match algorithm.

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Aim 4 (B.2.4)

Interpretation of the primary data into genotype lists and integration into matching algorithm to optimize placement of donors onto patient searches.

Activity:

During the past quarter there have been minor performance enhancements to the matching algorithm. An implementation in Java was developed and validated so that the HapLogic matching can be embedded in more applications where one-time match grade computation is required.

A search server for public searching was developed that uses a modified version of the matching algorithm facilitate a public web-searching interface.

B. Development of Science and Technology for Rapid Identification of Matched Donors

The primary goal of this project is to increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

Hypothesis 3 - Registry data on HLA allele and haplotype frequencies and on the nuances of HLA typing can be used to design computer algorithms to predict the best matched donor. (B.3)

Efforts of these Aims are to support the hypothesis that HLA frequency data and primary DNA data can be used to predict the best-matched donor. Approaches to insure data validation and provide public dissemination of results will be included.

Aim 1 (B.3.1)
Incorporate EM haplotype estimation logic into matching algorithm.

Activity:
A manuscript for publication of HLA analysis of the high-resolution typed donor cohort used for HapLogic was completed and an abstract was submitted for a talk at the ASHI conference.

The haplotype data used in HapLogic was refreshed to incorporate new high resolution typings from patient-directed and prospective projects. These new haplotype frequencies will be applied during the next quarter and then periodically on an ongoing basis as better haplotype frequency data becomes available.

Aim 2 (B.3.2)
Continue to enhance the EM algorithm to include additional loci and increased resolution for ethnic groups with input from consultants with expertise in population genetics.

Activity:
Additional work on a population comparison program that compares HLA haplotype and genotype frequencies at one, two, and three loci was completed.

An abstract was also submitted for a talk at ASHI on HLA analysis of a cohort of multiethnic donors.

Aim 3 (B.3.3)

Use the EM algorithm to predict haplotypes for matching probabilities (revised Benchmark analysis) and Optimal Registry Size Analysis.

Activity:
An abstract was submitted for a talk at the ASHI conference on 8/8 allele match rate prediction. 7/8 and 4/6 match rate predictions were added to the registry size program. An effort is underway to examine match rates for patients searching the cord registry using 6/6, 5/6, 4/6 match criteria who don't find matches in the adult donor registry using 8/8, 7/8 allele match criteria.

A manuscript for publication of a Greek Registry Size study with Dimitri Monos was completed. An abstract was submitted for a poster at the ASHI conference on the same topic.

An analysis of HLA and non-HLA factors on the patient populations was completed. Non-HLA factors examined the effect of race/ethnicity, age, and geography (center, ZIP code, geographical region) on the number of matches found. HLA factors analysis used the assignment of race using the Bayesian classifier and the classification of haplotypes into low, medium, and high frequency for each individual. A report was submitted to HRSA on this patient profiling.

Aim 4 (B.3.4)

Couple haplotype prediction methodology with donor demographic data (i.e., zip codes) to target recruitment to areas populated by individuals with underrepresented HLA phenotypes.

Activity:
A Bayesian classifier was developed to assign race/ethnic categories to individuals using haplotype frequencies from donor populations and the priors of the relative size of the donor populations. This algorithm gives the probability for each race/ethnicity overall and for each haplotype, allowing for multiple-race individuals. An abstract was submitted for a talk at the ASHI conference on this topic.

Aim 5 (B.3.5)

Develop a bioinformatics web site for frequency information.

Activity:
The data from the rare allele tally was updated and added to the new bioinformatics website (bioinformatics.nmdp.org).

Aim 6 (B.3.6)

Use NMDP's expert HLA consultants as resources to further improve the matching algorithm and donor identification software applications with the goal to maximize the ability of the software to identify the best donors for each patient.

Activity:
During the past quarter 169 HLA consultations were performed by the internal team of expert HLA Advisors. The adult donor and cord blood selections and prioritizations from the HLA consultations were logged into a tracking system and will be utilized to compare with the selections and sort order generated by the HapLogic software for each of the same patient searches. The final analysis is anticipated to begin after the end of the next quarter when sufficient data have accumulated.

B. Development of Science and Technology for Rapid Identification of Matched Donors

The primary goal of this project is to increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

Hypothesis 4 - Reducing the time and effort required to identify closely matched donors for patients in urgent need of HSC transplants will improve access to transplantation and patient survival in the context of a contingency response and routine patient care. (B.4)

Efforts of these Aims are to expand the NMDP network communications and develop centralized search management proficiency for use during contingency situations.

Aim 1 (B.4.1)

Expand NMDP's automated communication capabilities to further streamline the electronic exchange of information throughout the Network.

Activity:
This aim affects many applications at NMDP in part. They include:

- Electronic receipt of IDM results via FormsNet
- Electronic receipt of cooperative registry data via EMDIS
- Electronic receipt of NMDP member center data via STAR II Transaction Broker
- Electronic receipt of NMDP operational data into the SIP database
- Interaction of SEARCH Link and TRANS Link with the SIP database

FormsNet
The FormsNet 2.0 project has been initiated to combine the existing legacy Registry data entry system into the web-based FormsNet data entry application. This will improve efficiency by eliminating duplicate applications and QA processes, allowing for the sharing of code and resources with the CORD Link® and STAR Link® applications, and allow for development staff to take over positions currently held by contractors. The first phase of this project is to make the harmonized forms available to the Research data entry staff in the FormsNet application.

Work on the FormsNet 2.0 application is proceeding rapidly with the main data entry modules being mostly completed. The next step will be to start on the security, audit and form insert modules. The pre and post-disease form inserts are expected to be approved by August 2006.

STAR II Transaction Broker
Reference the update on STAR II found under Aim IIA 1.3.

SIP Database

As new information emerges from the increased electronic exchange of data, the SIP database must be modified to house new data elements. The SIP database facilitates management of the Search/Transplant process through data exchange with Donor Centers, Cord Blood Banks, Transplant Centers, etc. A new project was started to investigate the ability to unify all databases that contain data involved in the search-tracking and invoicing process migrate to SIP database. The goal is to unify various information systems under a single vision of the company business processes by modeling the corporate data in such a way that it would represent cohesive whole by eliminating unnecessary data redundancies while preserving efficient data access by various applications. The initial phase this past quarter was to begin the development of a conceptual data model.

SEARCH Link/TRANS Link

Ongoing maintenance occurred and improvements were made to both the SEARCH Link and TRANS Link applications. The main focus of the latest upgrade was to implement changes for the Cord Blood Confirmatory Typing Packages.

Aim 2 (B.4.2)

Develop central search management proficiency that can be utilized in contingency situations to assist transplant centers.

Activity:

NMDP provided centralized donor selection and search management for 35 patient searches at one transplant center. NMDP hired an additional Senior Central Search Management Coordinator to prepare for additional transplant center support. The team will travel during the next quarter to meet with transplant centers interested in the service, developing operational procedures customized to meet individual transplant center needs.

C. Immunogenetic Studies

The goal of this project is to increase understanding of the immunologic factors important in HSC transplantation.

Hypothesis 1 - HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantitate the influence of specific HLA mismatches. In contingency situations it will not be possible to delay transplant until a perfectly matched donor can be found. (C.1)

Efforts of this Aim will have important practical consequences for donor selection and patient management.

Aim 1 (C.1.1)

Evaluate HLA disparity and impact on HSC transplantation by adding selected pairs to the Donor/Recipient Pair project utilizing sample selection criteria that optimize the new data generated by the typing project.

Activity:
During the past quarter database design, development and testing continued on the Immunobiology Project Results (IPR) database. Scientific Services is working with a Buisness System Analyst (BSA) to define interfaces for the IPR database. This database is being developed to record the typing results of all immunobiology projects that utilize the NMDP research samples.

Final preparation of Sample Group 15 (SG15) will be completed early next quarter. This Sample Group consists of 600 Donor/Recipient sample pairs and 43 Cord/Recipient sample pairs. The CIBMTR Statistical Center reviewed and approved the data set for SG15. At the suggestion of the Statistical Center, SG15 will be limited to peripheral blood stem cell and cord blood transplant pairs due to the under representation of these graft sources in the current Donor/Recipient Pair project dataset. The period of performance for SG15 will be August 1, 2006 through November 30, 2006.

Data processing has been ongoing for sample groups 14, C1 and KIR sample group 2.

C. Immunogenetic Studies

The goal of this project is to increase understanding of the immunologic factors important in HSC transplantation.

Hypothesis 2 - Even when patient and donor are HLA matched, GVHD occurs, therefore, other loci may play a role. (C.2)

Efforts of this Aim will be to move technology forward from the current practice of locus level typing to high resolution typing, to disseminate information and protocols in an open source mechanism and to develop reference lines for use in individual laboratories.

Aim 1 (C.2.1)

Initiate the development of typing protocols for non-HLA immunogenetic loci, develop a lab network, implement database to capture non-HLA data and initiate analyses to evaluate genetic diversity in the transplant population.

Activity:

Bioinformatics and Scientific Services staff continued to refine the design of the Immunobiology Project Results (IPR) database for the capture of HLA and non-HLA data. The NMDP received reports of immunobiological test results including MHC microsatellites and cytokine genotypes generated through NMDP/CIBMTR approved studies. These data were validated for clinical outcome correlation and archived for transfer into the IPR database upon completion.

Aim 2 (C.2.2)

Establish a Related Pairs Research Repository; develop necessary operational procedures and supporting systems.

Activity:

During the past quarter, NMDP staff continued to prepare the study protocol and IRB application for implementation of the Related Pairs Repository. Discussions continued with CIBMTR staff to develop case selection procedures and a notification process for participating transplant centers. In addition, the specifications for necessary modifications to the existing Research Sample Repository inventory management software were prepared. The software updates are needed to facilitate the receipt, processing and accessioning of related pair samples into the

inventory. The software modifications will be implemented following IRB approval of the study protocol and application.

D. Clinical Research in Transplantation

The primary goal of this project is to create a platform that facilitates multicenter collaboration and data management. Many of the research protocols address issues important for managing the radiation exposure victim. Examples include exploration of alternative stem cell sources, acceleration of hematopoietic recovery, reduction of acute and chronic graft-versus-host disease, and others. Advancing the research capabilities facilitate a coordinated and effective contingency response.

Hypothesis 1 - (D.1)

Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.

Efforts of these Aims are for research targeting important transplant-related complications (e.g. GVHD or organ toxicity) or considering strategies that would allow broader application of transplantation to persons in need (e.g., use of HLA-mismatched cord blood for persons without a matched bone marrow donor).

Aim 1 (D.1.1)

Conduct observational research and interventional clinical trials.

Support for CIBMTR clinical trials

- **Prospective trials**
- **Data management systems**
- **Cord blood research**

Partnership with the intramural NIH transplant programs

Support for CIBMTR observational studies

Activity:

During this reporting period staff continued to develop templates and procedures for use in the management of clinical trials. A draft Manual of Procedures was created to support the Prospective trial activity. Planning for assessment of data management systems occurred during this period with a meeting scheduled in August 2006. Establishment of a Monitoring Board was initiated during this period. A draft charter and identification of potential board members also occurred.

Staff has begun work on the development of a clinical trial in the area of Cord blood research. The Primary Investigator for this trial is Dr. Juliet Barker of Sloan-Kettering Cancer Center. A protocol team was established with bi-monthly conference calls to develop the protocol.

Observational staff continued to work on various studies during this period. Nine of the seventeen working committees are supported by staff at the CIBMTR Minneapolis campus. During this period a Research Specialist was hired to provide assistance to the statistical staff in study activities.

D. Clinical Research in Transplantation

The primary goal of this project is to create a platform that facilitates multicenter collaboration and data management. Many of the research protocols address issues important for managing the radiation exposure victim. Examples include exploration of alternative stem cell sources, acceleration of hematopoietic recovery, reduction of acute and chronic graft-versus-host disease, and others. Advancing the research capabilities facilitate a coordinated and effective contingency response.

Hypothesis 1 - (D.1)

Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.

Efforts of these Aims are for research targeting important transplant-related complications (e.g. GVHD or organ toxicity) or considering strategies that would allow broader application of transplantation to persons in need (e.g., use of HLA-mismatched cord blood for persons without a matched bone marrow donor).

Aim 2 (D.1.2)

Support research with NMDP donors and for donor studies proposed by outside investigators.

Activity:
Susan Flesch was hired as the Sr. Research Specialist and started in this position on May 15, 2006. There are currently two protocols from outside investigators that are being supported by this position. Policies and procedures for support of research by outside investigators will be developed in conjunction with the development and implementation of these two protocols.

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Aim 3 (D.1.3)

Expand support for immunobiology research, statistical genetics and clinical research studies under CIBMTR Immunogenetics Working Committee.

Activity:

During the last quarter NMDP Scientific Services staff received two inquiries and one formal request for supplemental funding support of approved CIBMTR Immunobiology Working Committee (IBWC) studies. The inquiries were for reagent support for a study evaluating the impact of alloantibodies in sex mismatched transplants and a study investigating the impact of minor histocompatibility antigen disparity on transplant outcome. Formal requests are expected in the next quarter. The one formal request was for reagent and technician salary support for a study evaluating chemokine gene polymorphisms in HLA-A, B, C, DRB1 and DQB1 high resolution matched transplant pairs. The request is under review with an award expected in the next quarter.

In an effort to promote the activities and resources of the IBWC to the broader scientific community, NMDP Scientific Services staff prepared informational materials for distribution at scientific meetings. During the past quarter, the materials were distributed at a CIBMTR

exhibition booth during the 2006 Federation of Clinical Immunology Societies annual meeting in San Francisco, CA. The IBWC will continue to identify other promotional opportunities at scientific meetings on an ongoing basis and refine the informational materials as appropriate.

NATIONAL MARROW DONOR PROGRAM®

Creating Connections. Saving Lives.™

Grant Award N00014-05-1-0310

QUARTERLY PERFORMANCE / TECHNICAL REPORT

for

APRIL 1, 2006 to JUNE 30, 2006

Office of Naval Research

And

The National Marrow Donor Program
3001 Broadway Street N.E.
Minneapolis, MN 55413
1-800-526-7809

Grant Award N00014-05-1-0310
Performance Report
April 1, 2006 – June 30, 2006

National Marrow Donor Program®
HLA Typing for Bone Marrow Transplantation

Task 1: Product Validation

Description:
The objective of this study is to evaluate optimal short term storage parameters for stimulated and unstimulated leukapheresis (donor lymphocytes) and bone marrow products, including the type of storage media and the cell concentration, in addition to temperature and duration of storage before processing or infusion.

Project 1. Effects of Media Storage and Cell Concentration

Stimulated and unstimulated leukapheresis and bone marrow products that are representative of products collected and provided for NMDP transplant patients will be purchased. Aliquots of the product will be stored in different storage media at varying cell concentrations per mL of media. Standard graft characterization parameters will be tested.

Objectives:

1. Transportation factors: Determine the effects of different types of tissue media, nucleated cell concentration on CD34+ cell, CD3+ and total nucleated cell viability, and CFU-GM frequency during transport from collection sites to the transplant centers.

2. Overnight storage factors: Determine the effects of different type of tissue media, type of storage bags (gas permeable or non gas permeable), nucleated cell concentration on CD34+, CD3+ cell and total nucleated cell viability, and CFU-GM frequency during overnight storage.

Project 2. Effects of Time and Temperature

Stimulated and unstimulated leukapheresis and bone marrow products that are representative of products collected and provided for NMDP transplant patients will be purchased. Aliquots of the product will be stored at varying lengths of time and temperature. Standard graft characterization parameters will be tested.

Objectives:

1. Temperature factors: Determine the optimal short term storage temperature to preserve nucleated cell count, percent viable TNC, CD34+ and CD3+ cells, CFU-GM frequency and sterility.

2. Time factors: Determine the effect of time on nucleated cell count, percent viable TNC, CD34+ and CD3+ cells, CFU-GM frequency and sterility.

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Activity:

During the past quarter, Scientific Services staff worked with a panel of cell processing experts to revise the study design for the project. The panel recommended administering a survey on the "state-of-the-art" for cellular product collection and storage to further refine the study design. Scientific Services staff developed a survey that was distributed to the International Society for Cellular Therapy (ISCT) membership. The NMDP received 45 responses from U.S. centers and 31 responses from international centers. The data received from the survey were shared with the expert panel and based on their recommendations the NMDP finalized the Scope of Work for the project. The Request For Proposals (RFP) in support of the project was finalized, reviewed and subsequently released on June 6, 2006. The question and answer period was completed June 14, 2006. Responses to the RFP are due early next quarter.

Government Signature _____ Date _____

Product Validation

Grant Award N00014-05-1-0310
Quarterly Performance / Technical Report
April 1, 2006 – June 30, 2006

National Marrow Donor Program®
HLA Typing for Bone Marrow Transplantation

Task 2: Validation of the Expectation – Maximization (EM) Algorithm

Description:

The NMDP has developed an algorithm that "predicts' high resolution HLA typing results on donor samples that exist in the Registry with only low or intermediate results reported. A modified version of this algorithm predicts HLA results at loci where there are no typings based on existing typings at other loci and the ethnic-specific haplotype frequencies observed in the population.

It is our intention to incorporate this logic into the mechanisms used to select matched donors for patient searches. Incorporation of this logic would improve the specificity of donors that appear on patient's searches, which then decreases the costs and time necessary to identify the optimally matched donor. This logic will also be used to provide estimates of the likelihood of finding matched donors in the Registry including matching at loci where some donors in the Registry do not currently have typings.

A portion of the funding would be used to assist in the validation of the NMDP algorithm by selecting donors randomly from our Registry who have low or intermediate DRB1 typing results and using the algorithm to predict the high resolution results. The HLA typing results would be used to validate the accuracy of this method in an unbiased data set.

The remaining portion of the funding would be used to test the ability of the algorithm to predict KIR ligand mismatching in the absence of existing HLA-C locus results. Randomly selected donors from the Registry without HLA-C would be run through a modified version of the algorithm to predict the C locus KIR ligand status. The HLA intermediate resolution typing would validate the accuracy of this method in an unbiased data set.

A laboratory would perform the high resolution HLA-DRB1 testing and/or intermediate resolution HLA-B and C from stored samples of the donors. Quality control and performance criteria will be monitored by a Scientific Services Specialist. The results will be analyzed by a programmer in the Bioinformatics group to verify the accuracy of each prediction technique.

In addition to assisting with the validation of the algorithm, this typing project has potential to impact subsequent patient searches simply due to the increased level of resolution for the Registry donors whose typings have been upgraded. A portion of this typing may be selected on behalf of searching patients in order to further validate the approach and provide direct positive impact on these searches.

Activity:

No activity.